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External-beam radiotherapy for differentiated thyroid cancer locoregional control: A statement of the American Head and Neck Society

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Abstract

The use of external-beam radiotherapy (EBRT) in differentiated thyroid cancer (DTC) is debated because of a lack of prospective clinical data, but recent retrospective studies have reported benefits in selected patients. The Endocrine Surgery Committee of the American Head and Neck Society provides 4 recommendations regarding EBRT for locoregional control in DTC, based on review of literature and expert opinion of the authors. (1) EBRT is recommended for patients with gross residual or unresectable locoregional disease, except for patients <45 years old with limited gross disease that is radioactive iodine (RAI)-avid. (2) EBRT should not be routinely used as adjuvant therapy after complete resection of gross disease. (3) After complete resection, EBRT may be considered in select patients >45 years old with high likelihood of microscopic residual disease and low likelihood of responding to RAI. (4) Cervical lymph node involvement alone should not be an indication for adjuvant EBRT.

Keywords

radiotherapy; radiation; thyroid cancer; papillary; follicular

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Introduction

The role of external-beam radiotherapy (EBRT) in differentiated thyroid cancer (DTC) is debated because of a lack of prospective clinical data, as well as inhomogeneity and conflicting results in the existing retrospective data. It is optimally used in a small subset of patients with thyroid cancer with aggressive locoregional disease. A single randomized prospective trial in Germany failed to recruit adequate patients and only 26 received EBRT.[1] However, a mounting number of retrospective studies have been reported, including several recent studies showing significant benefit for EBRT in select patients.[2–4] The Endocrine Surgery Committee of the American Head and Neck Society (AHNS) here provides recommendations regarding the use of EBRT for locoregional control in DTC, based on review of the literature and expert opinion of the authors.

The goal of EBRT in DTC is to optimize locoregional control while limiting treatment toxicity. For most patients with DTC, surgery and radioactive iodine (RAI) are effective in achieving locoregional control. However, in cases in which surgery or RAI are less effective, EBRT may be recommended. The intent of treatment with EBRT is generally categorized as definitive (for curative treatment of gross disease), adjuvant (for treatment of presumed residual disease after surgery), or palliative (for symptom control). However, in DTC, these categories are often blurred, as patients with unresectable disease or distant metastases may still have a fair overall prognosis, and they may suffer consequences of uncontrolled disease in the central neck.[5] For patients with distant metastases, the importance of locoregional control should be weighed against the overall prognosis and the potential toxicities of EBRT. For example, some patients with RAI-avid lung metastases and residual or unresectable neck disease may be recommended neck EBRT with doses of 60 to 70 Gy, whereas other patients with uncontrolled non–RAI-avid lung metastases and symptomatic neck disease may be recommended palliative neck EBRT with lower doses. We will focus our discussion on EBRT applications using 60 to 70 Gy, but for patients with poor prognosis, lower palliative doses may be recommended.

The risk of locoregional recurrence or progression in DTC is related to many well-described clinicopathologic risk factors. These include older age (≥45 years old), unfavorable histology (poorly differentiated, tall cell, columnar, insular, Hurthle cell), low RAI uptake, and locally invasive disease.[6,7] Recent data suggests that stage T4a disease (by American Joint Committee on Cancer 7th edition) with gross extrathyroidal extension is strongly associated with risk of locoregional recurrence, whereas stage T3b disease with minimal extrathyroidal extension is not significantly associated with locoregional recurrence.[8,9] Nixon et al[10] reported that microscopic extrathyroidal extension alone (pathologic T3b) was not a negative prognostic factor in patients with clinical stage T1 or T2 DTC who underwent thyroidectomy. The presence of gross residual disease or positive margins after thyroidectomy, however, significantly increases the risk of recurrence or progression.[11,12] There is clearly a very high risk of locoregional recurrence in cases in which the tumor is shaved off the recurrent laryngeal nerve, trachea, or larynx, presumably leaving residual microscopic disease.[13] Finally, if a patient is undergoing revision surgery for recurrent disease, he or she is at risk for additional recurrences in the future.

In this report, we will describe the data supporting the use of EBRT in patients with gross residual or unresectable disease. We will also consider the use of EBRT as adjuvant therapy in select patients after complete resection of gross disease, specifically in older patients with high likelihood of microscopic residual disease and low likelihood of responding to RAI. To identify which patients fall into these categories, we will also summarize the surgical and RAI considerations regarding locally invasive disease.

Materials and Methods

A writing group was convened by the Endocrine Surgery Committee of the AHNS, and this group met in person and by telephone and email to determine the scope of the topic and outline relevant subtopics. The group decided to focus on EBRT directed to the neck for papillary, follicular, or Hurthle cell carcinomas. We therefore did not address EBRT for palliation of distant metastases, or for treatment of anaplastic, poorly differentiated, or medullary thyroid cancers. However, there is a spectrum of well to poorly differentiated thyroid cancers, and most of the relevant studies included patients with refractory or RAI-resistant cancers that are presumably less well-differentiated. A PubMed search was conducted to identify literature from the years 2000 to 2014 using the following terms: differentiated thyroid cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, Hurthle cell carcinoma, external-beam radiation, radiotherapy, local control, (loco)regional control, extrathyroidal extension, and nodal metastases. Key articles published before the year 2000 were selectively included. Current guidelines of the American Thyroid Association (ATA) and AHNS were reviewed and referenced, and additional recommendations were developed by the writing group to address areas where existing guidelines were unclear. The first draft was written over the course of 6 months, then revised by the writing group and submitted to the AHNS Endocrine Surgery Committee for further feedback. After endorsement by the Endocrine Surgery Committee, it was submitted to the AHNS Quality of Care Committee and the AHNS governing council who reviewed and endorsed it in its current form.

Recommendations

Gross residual or unresectable disease

Recommendation #1: EBRT is recommended for patients with gross residual or unresectable locoregional disease, except for patients <45 years old with limited gross disease that is RAI-avid.

Locally invasive thyroid cancer may involve the strap muscles, recurrent laryngeal nerve, trachea, larynx, esophagus, or major vessels.[13] With careful preoperative evaluation and planning, most cases of invasive disease can be resected without gross residual disease, but there will inevitably be some cases of unresectable disease or gross residual disease not amenable to further resection.[13] This occurs more frequently in the setting of recurrent disease. In addition, there are also some patients unwilling to undergo aggressive aerodigestive tract surgery with sacrifice of function or who have medical comorbidities making surgery unwise. In these patients, it is important to decide the intent of treatment upfront (definitive vs palliative), as the likelihood of locoregional control with EBRT is

related to dose, but toxicities also increase with dose.[14] In general, the use of intensity-modulated radiotherapy (IMRT) with doses >60 Gy results in higher likelihood of long-term control.[2,15]

Many retrospective studies show evidence of long-term locoregional control with the use of EBRT in patients with gross residual or unresectable DTC.[3,12,16–20] In a large Hong Kong study, patients with papillary thyroid cancer with gross residual disease ($n = 217$) had 10-year locoregional recurrence-free survival of 63% with EBRT compared to 24% without EBRT ($p < .001$).[3] At Memorial Sloan Kettering Cancer Center, 66 patients with gross non-anaplastic nonmedullary thyroid cancer were treated with EBRT, resulting in 3-year local progression-free survival of 73% without concurrent chemotherapy and 90% with concurrent chemotherapy (although the effect of adding chemotherapy was greatest in patients with poorly differentiated histology).[17,18] At Princess Margaret Cancer Centre, the 5-year local recurrence-free rate was 62% in 33 patients with gross DTC who received EBRT.[16] Finally, Schwartz et al[12] reported that, of a cohort of 15 patients with gross DTC treated at MD Anderson with EBRT, 3 had a partial response and 4 had a sustained complete response. A phase II clinical trial is currently open at Memorial Sloan Kettering Cancer Center for patients with gross recurrent or unresectable nonanaplastic thyroid cancer, combining EBRT to 70 Gy with low-dose adriamycin (NCT01882816).

In young patients (<45 years old) with limited gross residual disease that is RAI-avid, EBRT is usually not recommended. These patients have lower risk for locoregional progression and, in the setting of small-volume disease, RAI alone may achieve excellent control.[5,21,22] Furthermore, EBRT carries a small additional risk of late toxicities or second malignancy. The risk of radiation-induced malignancy after RAI or EBRT is generally low but it increases with longer elapsed time after treatment and with younger age of irradiation.[23–25] Although RAI alone is not often successful in treatment of cervical nodal metastases measuring >1 cm, such nodal metastases are usually amenable to neck dissection.[21]

Microscopic residual disease after complete resection

Recommendation #2: EBRT should not be routinely used as adjuvant therapy after complete resection of gross disease.

The use of adjuvant EBRT after complete resection of invasive DTC is highly debated, with no routine indications and varying opinions and practices at different institutions. For each patient, there are multiple surgical and pathologic factors contributing to the risk of microscopic residual disease, and there are several treatment options that impact long-term locoregional control, including RAI, EBRT, and further surgery. Therefore, we strongly recommend multidisciplinary discussion of each of these cases. To this end, we will first summarize the surgical and RAI considerations regarding adjuvant therapy for DTC, specifically focusing on the risk of microscopic residual disease and the likelihood of responding to RAI. We will then consider the specific data and recommendations regarding adjuvant EBRT.

Surgical considerations regarding adjuvant therapy for differentiated thyroid cancer

Surgical considerations regarding locally invasive DTC have been recently summarized in an AHNS consensus statement by Shindo et al.[13] Briefly, as noted above, invasive thyroid cancer may involve the strap muscles, recurrent laryngeal nerve, and/or trachea; less commonly, it may involve the larynx, esophagus, or major vessels. Although most cases of invasive disease can be resected without gross residual disease, a significant number will have microscopic residual disease. In general, tumors with anterior extension to the strap muscles are considered resectable with minimal morbidity and without need for reconstruction. Tumors with posterior extension can be more challenging. The recurrent laryngeal nerve (RLN) may be sacrificed if it is encased by tumor and there is pre-operative ipsilateral vocal fold paresis.[26] However, if there is ipsilateral function, the tumor may be shaved off to spare the RLN as long as all gross disease is removed; in this case, there is risk of microscopic residual disease.[27] If a short segment of the trachea is involved with minimal cartilage invasion, a tracheal shave excision is considered appropriate, but circumferential sleeve resection may be indicated for more significant cartilage invasion or intraluminal invasion.[11,28] After tracheal shave excision, there is a high risk of microscopic residual disease. In the setting of esophageal or laryngeal involvement, there are similar considerations regarding microscopic disease after limited resection of involved esophageal muscularis or shave excision of the larynx. In cases in which the jugular vein is involved by extensive nodal extracapsular spread, the vein may be excised without reconstruction when the contralateral vein is patent, but there may again be risk of microscopic disease in the neck.[29]

In summary, there is a higher likelihood of microscopic residual disease in cases in which the tumor is shaved off the RLN, trachea, or larynx, or if a limited resection of esophageal muscularis or sacrifice of the jugular vein is required. These scenarios may occur in the setting of gross extrathyroidal extension, gross extracapsular spread, or revision surgery for persistent or recurrent disease. When margin status can be assessed pathologically, there is often a positive margin in these settings, which is a marker of microscopic residual disease.[4] However, in order to assess a patient's likelihood of microscopic disease, it is important for the radiation oncologist to communicate directly with the surgeon to correlate pathologic findings with operative findings. This is also critical for radiation treatment planning, as the pathology report often cannot convey the exact location of the most invasive disease.

Considerations regarding adjuvant radioactive iodine therapy for differentiated thyroid cancer

Considerations regarding the use of adjuvant RAI for DTC are well-described and summarized in the updated ATA guidelines.[30] Briefly, iodine is taken up by thyroid epithelial cells and well-differentiated thyroid cancer cells, so the beta emitter ^{131}I is an effective targeted radiopharmaceutical for DTC. RAI therapy can be used after primary surgery for ablation of the normal thyroid remnant (50–75 mCi), for adjuvant therapy for risk of microscopic disease (100–150 mCi), or for therapy of macroscopic disease (high doses, often repeated).[21,22] In several studies, adjuvant RAI has been shown to decrease recurrence rates in DTC.[21,22,31–33] Tuttle et al[22] showed that, even when post-RAI whole body scans showed residual small-volume disease in the neck, thyroid-stimulating hormone-

stimulated RAI resulted in 70% locoregional control with a median of 2.7 years of follow-up.[22] Furthermore, RAI after primary surgery may also improve overall survival in patients with intermediate to high-risk features.[33,34] Therefore, after primary surgery, consideration for RAI therapy is currently recommended by the ATA for patients with stage T2 to T4 or N1 or M1 disease.[30]

RAI therapy is inherently limited by the avidity of thyroid cancer cells for iodine. Therefore, the likelihood of responding to RAI is significantly decreased in patients with unfavorable histology (poorly differentiated, tall cell, columnar, insular, and Hurthle cell carcinoma),[6] older age, recurrent disease (especially after prior RAI), or low RAI uptake on whole body scan in a patient with known residual disease.[35] In addition, high fluorodeoxyglucose (FDG) uptake on FDG-positron emission tomography (PET) scan also correlates with poor RAI avidity and efficacy.[36] In patients with rising thyroglobulin but negative RAI scans, FDG-PET is 98% effective in detecting recurrent disease, and FDG-avid lesions do not respond to RAI therapy.[36–38] Notably, patients with unfavorable histology still show benefit of RAI, so it is usually indicated for these patients even if they receive adjuvant EBRT.[39]

Adjuvant external-beam radiotherapy after complete resection of invasive differentiated thyroid cancer

Recommendation #3: After complete resection, EBRT may be considered in select patients older than 45 years old with high likelihood of microscopic residual disease and low likelihood of responding to RAI. This scenario may occur in the setting of gross extrathyroidal extension or with revision surgery for persistent or recurrent disease.

In older patients who have undergone complete resection but have high likelihood of microscopic residual disease and low likelihood of responding to RAI, adjuvant treatment with EBRT may be considered. There are several recent studies that support the use of adjuvant EBRT in these select patients.[2–4,40,41] In a Korean study of 68 patients who underwent shave excision of a thyroid tumor off the trachea, EBRT significantly decreased locoregional recurrence from 51% to 8% ($p < .01$).[4] Chow et al[3] showed that patients with resected stage pT4a papillary thyroid cancer ($n = 131$) had better 10-year local failure-free survival after EBRT plus RAI (88%) compared to RAI alone (72%) or EBRT alone (60%), similar to previous studies by Farahati et al[40] and Kim et al.[42] Those patients with stage pT4a disease seemed to derive more benefit from EBRT than those with stage pT3b, as expected. In addition, patients with positive margins also had improved local failure-free survival after EBRT plus RAI (90%) compared to RAI alone (80%) or EBRT alone (57%).[3] The combination of EBRT plus RAI will be discussed further below. A recent update from Princess Margaret Cancer Centre showed significantly higher 10-year cause-specific survival and local relapse-free survival in patients >60 years old with extrathyroidal extension and no gross residual disease who received EBRT ($n = 70$).[2] Notably, this did not hold true for all patients >45 years old, but the number of patients was small and patients with microscopic extrathyroidal extension (pT3b) were included.[2] For younger patients, especially those <45 years old, EBRT is usually not recommended after complete resection, as these patients have a lower risk of locoregional recurrence, and RAI and/or further surgery are likely to achieve

long-term control. As noted above, there is also increased concern in younger patients regarding the risk of late toxicities and second malignancies.

Recommendation #4: Cervical lymph node involvement alone should not be an indication for adjuvant external-beam radiotherapy.

After complete resection of DTC, patients with cervical nodal metastases have a risk of microscopic residual nodal disease. However, as noted above, adjuvant RAI is usually quite effective at clearing microscopic residual disease in the nodes.[21,22] In addition, recurrences of DTC in the nodes are more easily salvaged (with neck dissection) than recurrences in the thyroid bed. Therefore, after complete resection, cervical lymph node involvement alone should not be an indication for EBRT, but EBRT may be considered if there is extensive extracapsular spread with high risk of microscopic residual disease.

Radiotherapy technique and toxicities

EBRT target volumes and doses are custom-designed for each patient according to their risks for local and regional recurrence. The pattern of lymphatic spread in thyroid cancers is different than other head and neck cancers, with the first echelon of nodal drainage to level VI, then levels III, IV, and II.[43] Typically, there is not involvement of level I or retropharyngeal nodes except in the setting of recurrence. The recommended therapeutic doses of EBRT for DTC are similar to other head and neck cancers (Table 1). These cumulative doses are 66 to 70 Gy for gross disease or areas of positive margin or shave excision, approximately 60 Gy for high-risk microscopic disease areas (including the thyroid bed, tracheoesophageal groove, and level VI), and approximately 54 Gy for low-risk microscopic disease areas (including uninvolved levels II–V and VII).[44] We recommend a fraction size of 2 Gy per fraction or less, given the potential toxicities of larger fractions to the larynx and esophagus. The use of IMRT is recommended in order to achieve these different targeted dose levels and to spare the normal tissues, and image guidance is recommended when available to improve setup accuracy.[12,18] Given the option of salvage neck dissection for DTC, some expert radiation oncologists now consider limiting EBRT volumes to gross disease and high-risk microscopic disease areas within the central neck in some cases (sparing low-risk nodal areas), which may help limit toxicities of treatment.[45]

Toxicities of neck EBRT include common acute toxicities and uncommon chronic/late toxicities. The acute toxicities include mucositis (grade 3 in about 20%), dermatitis (grade 3 in 12%), dysphagia (grade 3 in 17%), and hoarseness.[17] Some patients will require short-term enteral feeding support via percutaneous gastrostomy or nasogastric tube, but with IMRT only about 5% will require long-term gastrostomy tube for dysphagia.[17,18] Other chronic toxicities may include neck fibrosis, chronic laryngeal edema (in about 3%), and esophageal or tracheal stenosis (in about 2%).[12,18] Stenosis requiring esophageal or tracheal dilatation was found to be less frequent after IMRT compared to 3D conformal radiotherapy.[12]

Combination of external-beam radiotherapy with other therapies

The combination of EBRT and RAI often generates confusion because of the lack of evidence regarding when and how these therapies should be combined. In general, the

indications for RAI are summarized by the ATA and are considered separately from EBRT. After primary surgery, consideration for RAI therapy is currently recommended for patients with stage T2 to T4 or N1 or M1 disease.[30] RAI is also frequently recommended for patients with recurrent or metastatic disease. As noted above, EBRT is more likely to be considered in patients with a lower chance of responding to RAI, such as those with unfavorable histology, older age, recurrent disease, high FDG uptake, and/or low RAI uptake in known residual disease.[35] There is no consensus regarding the optimal sequence of EBRT and RAI, but this may depend on the volume of gross residual disease and the likelihood of RAI response. In many cases, the presence of bulky gross disease and/or low likelihood of responding to RAI would favor scheduling EBRT first.[30]

The combination of EBRT with other systemic therapies is also a consideration as new therapies emerge for thyroid cancer. Several targeted kinase inhibitors have recently shown efficacy for RAI-refractory thyroid cancer including lenvatinib, sorafenib, pazopanib, and BRAF inhibitors.[46–49] In particular, lenvatinib recently demonstrated progression-free survival of 18 months in this population and received Food and Drug Administration approval in 2015.[46] However, common toxicities of kinase inhibitors may overlap with EBRT toxicities, including fatigue, decreased appetite, weight loss, nausea, stomatitis, and rash. There is also concern for potential serious adverse effects of these drugs. For these reasons, we recommend that EBRT at this time should only be used in combination with kinase inhibitors for thyroid cancer in the setting of clinical trials. In the future, molecular testing for genetic alterations, such as mutations in BRAF or the telomerase reverse transcriptase promoter or translocations with anaplastic lymphoma kinase, may allow for more personalized assessment of recurrence risk and selection of targeted therapies, RAI and/or EBRT.[50–52]

Several recent publications show promise for using other focal therapies such as radiofrequency ablation or percutaneous ethanol injection for locoregional recurrence of DTC.[53–58] In addition, high-intensity focused ultrasound has been used for ablation of benign thyroid nodules and may have potential for use in DTC.[59,60] However, these techniques are outside the scope of this article and should only be used as an alternative to EBRT in highly selected cases.

Conclusion

EBRT is a valuable treatment modality for improving locoregional control in patients with invasive DTC who may not achieve locoregional control with surgery and/or RAI. This includes patients with unresectable or gross residual disease, except for younger patients with limited gross disease that is RAI-avid. It also may include select older patients who have undergone complete resection but have high likelihood of microscopic residual disease and low likelihood of response to RAI. There is higher likelihood of microscopic residual disease in cases in which the tumor is shaved off the RLN, trachea, or larynx, which may occur in the setting of gross extrathyroidal extension or revision surgery for persistent or recurrent disease. Positive margins are also a marker for microscopic residual disease. There is lower likelihood of response to RAI in patients with unfavorable histology, older age, recurrent disease, low RAI uptake on whole body scan, or high FDG uptake on PET scan.

Given the lack of clear indications for EBRT after complete resection, we recommend multidisciplinary discussion of these cases.

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References

1. Biermann M, Pixberg M, Riemann B, et al. Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer – results after 874 patient-years of follow-up in the MSDS-trial. Nuklearmedizin. 2009; 48:89–98. quiz N15. [PubMed: 19322503]
2. Brierley J, Tsang R, Panzarella T, Bana N. Prognostic factors and the effect of treatment with radioactive iodine and external beam radiation on patients with differentiated thyroid cancer seen at a single institution over 40 years. Clin Endocrinol (Oxf). 2005; 63:418–427. [PubMed: 16181234]
3. Chow SM, Yau S, Kwan CK, Poon PC, Law SC. Local and regional control in patients with papillary thyroid carcinoma: specific indications of external radiotherapy and radioactive iodine according to T and N categories in AJCC 6th edition. Endocr Relat Cancer. 2006; 13:1159–1172. [PubMed: 17158761]
4. Keum KC, Suh YG, Koom WS, et al. The role of postoperative external-beam radiotherapy in the management of patients with papillary thyroid cancer invading the trachea. Int J Radiat Oncol Biol Phys. 2006; 65:474–480. [PubMed: 16542796]
5. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006; 91:2892–2899. [PubMed: 16684830]
6. Volante M, Landolfi S, Chiusa L, et al. Poorly differentiated carcinomas of the thyroid with trabecular, insular, and solid patterns: a clinicopathologic study of 183 patients. Cancer. 2004; 100:950–957. [PubMed: 14983490]
7. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. Laryngoscope. 2004; 114:393–402. [PubMed: 15091208]
8. Radowsky JS, Howard RS, Burch HB, Stojadinovic A. Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. Thyroid. 2014; 24:241–244. [PubMed: 23713855]
9. Rivera M, Ricarte–Filho J, Tuttle RM, et al. Molecular, morphologic, and outcome analysis of thyroid carcinomas according to degree of extrathyroid extension. Thyroid. 2010; 20:1085–1093. [PubMed: 20860430]
10. Nixon IJ, Ganly I, Patel S, et al. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. Surgery. 2011; 150:1242–1249. [PubMed: 22136847]
11. Kowalski LP, Filho JG. Results of the treatment of locally invasive thyroid carcinoma. Head Neck. 2002; 24:340–344. [PubMed: 11933175]
12. Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. Int J Radiat Oncol Biol Phys. 2009; 74:1083–1091. [PubMed: 19095376]
13. Shindo ML, Caruana SM, Kandil E, et al. Management of invasive well-differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHNS consensus statement Head Neck. 2014; 36:1379–1390. [PubMed: 24470171]
14. Ford D, Giridharan S, McConkey C, et al. External beam radiotherapy in the management of differentiated thyroid cancer. Clin Oncol (R Coll Radiol). 2003; 15:337–341. [PubMed: 14524487]
15. Rosenbluth BD, Serrano V, Happersett L, et al. Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. Int J Radiat Oncol Biol Phys. 2005; 63:1419–1426. [PubMed: 16154712]

16. Brierley, JD.; Schwartz, DL.; Tsang, RW. External beam radiotherapy for thyroid malignancy. In: Randolph, GW., editor. Surgery of the thyroid and parathyroid glands. Philadelphia, PA: Elsevier; 2013.
17. Romesser PB, Sherman EJ, Shaha AR, et al. External beam radiotherapy with or without concurrent chemotherapy in advanced or recurrent non-anaplastic non-medullary thyroid cancer. J Surg Oncol. 2014; 110:375–382. [PubMed: 24961938]
18. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan–Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys. 2009; 73:795–801. [PubMed: 18676097]
19. Sheline GE, Galante M, Lindsay S. Radiation therapy in the control of persistent thyroid cancer. Am J Roentgenol Radium Ther Nucl Med. 1966; 97:923–930.
20. Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D. External radiotherapy in thyroid cancers. Cancer. 1985; 55(9 Suppl):2062–2071. [PubMed: 3919920]
21. Tuttle RM, Rondeau G, Lee NY. A risk-adapted approach to the use of radioactive iodine and external beam radiation in the treatment of well-differentiated thyroid cancer. Cancer Control. 2011; 18:89–95. [PubMed: 21451451]
22. Tuttle RM, Lopez N, Leboeuf R, et al. Radioactive iodine administered for thyroid remnant ablation following recombinant human thyroid stimulating hormone preparation also has an important adjuvant therapy function. Thyroid. 2010; 20:257–263. [PubMed: 20187781]
23. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab. 2008; 93:504–515. [PubMed: 18029468]
24. Rubino C, de Vathaire F, Dottorini ME, et al. Second primary malignancies in thyroid cancer patients. Br J Cancer. 2003; 89:1638–1644. [PubMed: 14583762]
25. Ng AK, Bernardo MV, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood. 2002; 100:1989–1996. [PubMed: 12200357]
26. Chiang FY, Lin JC, Lee KW, et al. Thyroid tumors with preoperative recurrent laryngeal nerve palsy: clinicopathologic features and treatment outcome. Surgery. 2006; 140:413–417. [PubMed: 16934603]
27. Nishida T, Nakao K, Hamaji M, Kamiike W, Kurozumi K, Matsuda H. Preservation of recurrent laryngeal nerve invaded by differentiated thyroid cancer. Ann Surg. 1997; 226:85–91. [PubMed: 9242342]
28. Honings J, Stephen AE, Marres HA, Gaissert HA. The management of thyroid carcinoma invading the larynx or trachea. Laryngoscope. 2010; 120:682–689. [PubMed: 20213659]
29. Dulguerov P, Soulier C, Maurice J, Faidutti B, Allal AS, Lehmann W. Bilateral radical neck dissection with unilateral internal jugular vein reconstruction. Laryngoscope. 1998; 108(11 Pt 1): 1692–1696. [PubMed: 9818828]
30. Cooper DS, Doherty GM, et al. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19:1167–1214. [PubMed: 19860577]
31. Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am. 2008; 37:457–480. [PubMed: 18502337]
32. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994; 97:418–428. [PubMed: 7977430]
33. Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab. 1992; 75:714–720. [PubMed: 1517360]
34. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006; 16:1229–1242. [PubMed: 17199433]

35. Fatourechi V, Hay ID, Javedan H, Wiseman GA, Mullan BP, Gorman CA. Lack of impact of radioiodine therapy in Tg-positive, diagnostic whole-body scan-negative patients with follicular cell-derived thyroid cancer. J Clin Endocrinol Metab. 2002; 87:1521–1526. [PubMed: 11932275]
36. Wang W, Larson SM, Tuttle RM, et al. Resistance of [18f]-fluorodeoxyglucose-avid metastatic thyroid cancer lesions to treatment with high-dose radioactive iodine. Thyroid. 2001; 11:1169–1175. [PubMed: 12186505]
37. Finkelstein SE, Grigsby PW, Siegel BA, Dehdashti F, Moley JF, Hall BL. Combined [18F]fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) for detection of recurrent, 131I-negative thyroid cancer. Ann Surg Oncol. 2008; 15:286–292. [PubMed: 17882493]
38. Wang W, Larson SM, Fazzari M, et al. Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab. 2000; 85:1107–1113. [PubMed: 10720047]
39. Jung TS, Kim TY, Kim KW, et al. Clinical features and prognostic factors for survival in patients with poorly differentiated thyroid carcinoma and comparison to the patients with the aggressive variants of papillary thyroid carcinoma. Endocr J. 2007; 54:265–274. [PubMed: 17379963]
40. Farahati J, Reiners C, Stuschke M, et al. Differentiated thyroid cancer. Impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). Cancer. 1996; 77:172–180. [PubMed: 8630926]
41. O'Connell ME, A'Hern RP, Harmer CL. Results of external beam radiotherapy in differentiated thyroid carcinoma: a retrospective study from the Royal Marsden Hospital. Eur J Cancer. 1994; 30A:733–739. [PubMed: 7917529]
42. Kim TH, Yang DS, Jung KY, Kim CY, Choi MS. Value of external irradiation for locally advanced papillary thyroid cancer. Int J Radiat Oncol Biol Phys. 2003; 55:1006–1012. [PubMed: 12605980]
43. Kupferman ME, Patterson M, Mandel SJ, LiVolsi V, Weber RS. Patterns of lateral neck metastasis in papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg. 2004; 130:857–860. [PubMed: 15262763]
44. Rao, SSD.; Riaz, N.; Lee, NY.; Foote, RL. Thyroid Cancer Lee NY, Lu JJ, editors Target volume delineation and field setup. Heidelberg, Berlin: Springer–Verlag; 2013. p. 59-64.
45. Lee, N. Target volume delineation and the evolving role of external beam radiotherapy for thyroid cancer. Presented at the American Society for Radiation Oncology; Annual Meeting. San Francisco, CA. 2014.
46. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015; 372:621–630. [PubMed: 25671254]
47. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol. 2010; 11:962–972. [PubMed: 20851682]
48. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014; 384:319–328. [PubMed: 24768112]
49. Brose, M.; Cabanillas, M.; Cohen, E. The European Cancer Congress. Amsterdam: Elsevier; 2013. An open-label, multi-center phase 2 study of the BRAF inhibitor vemurafenib in patients with metastatic or unresectable papillary thyroid cancer (PTC) positive for the BRAF V600 mutation and resistant to radioactive iodine.
50. Liu X, Bishop J, Shan Y, et al. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. Endocr Relat Cancer. 2013; 20:603–610. [PubMed: 23766237]
51. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013; 309:1493–1501. [PubMed: 23571588]
52. Demeure MJ, Aziz M, Rosenberg R, Gurley SD, Bussey KJ, Carpten JD. Whole-genome sequencing of an aggressive BRAF wild-type papillary thyroid cancer identified EML4-ALK translocation as a therapeutic target. World J Surg. 2014; 38:1296–1305. [PubMed: 24633422]
53. Lee SJ, Jung SL, Kim BS, et al. Radiofrequency ablation to treat locoregional recurrence of well-differentiated thyroid carcinoma. Korean J Radiol. 2014; 15:817–826. [PubMed: 25469095]

54. Lim HK, Baek JH, Lee JH, et al. Efficacy and safety of radiofrequency ablation for treating locoregional recurrence from papillary thyroid cancer. Eur Radiol. 2015; 25:163–170. [PubMed: 25199815]

55. Guenette JP, Monchik JM, Dupuy DE. Image-guided ablation of postsurgical locoregional recurrence of biopsy-proven well-differentiated thyroid carcinoma. J Vasc Interv Radiol. 2013; 24:672–679. [PubMed: 23622038]

56. Vannucchi G, Covelli D, Perrino M, De Leo S, Fugazzola L. Ultrasound-guided percutaneous ethanol injection in papillary thyroid cancer metastatic lymph-nodes. Endocrine. 2014; 47:648–651. [PubMed: 24610207]

57. Shin JE, Baek JH, Lee JH. Radiofrequency and ethanol ablation for the treatment of recurrent thyroid cancers: current status and challenges. Curr Opin Oncol. 2013; 25:14–19. [PubMed: 23079931]

58. Fontenot TE, Deniwar A, Bhatia P, Al-Qurayshi Z, Randolph GW, Kandil E. Percutaneous ethanol injection vs reoperation for locally recurrent papillary thyroid cancer: a systematic review and pooled analysis. JAMA Otolaryngol Head Neck Surg. 2015; 141:512–518. [PubMed: 25928119]

59. Maloney E, Hwang JH. Emerging HIFU applications in cancer therapy. Int J Hyperthermia. 2015; 31:302–309. [PubMed: 25367011]

60. Esnault O, Franc B, Menegaux F, et al. High-intensity focused ultrasound ablation of thyroid nodules: first human feasibility study. Thyroid. 2011; 21:965–973. [PubMed: 21834683]

Table 1

External beam radiotherapy dose recommendations.

Target dose	Target description
70 Gy	Gross disease
66 Gy	Areas of positive surgical margin or shave excision
60 Gy	Areas with high risk of microscopic disease (including thyroid bed, tracheoesophageal groove, and level VI cervical nodes)
54 Gy	Areas with low risk of microscopic disease (including uninvolved level II–V and VII nodes)

Approximate cumulative doses are shown, with recommended fraction size of 2 Gy per fraction or less.[44] It is reasonable to consider limiting EBRT volumes to gross disease and high-risk microscopic disease areas within the central neck in some cases (sparing low-risk areas areas).[45]